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San Francisco, CA
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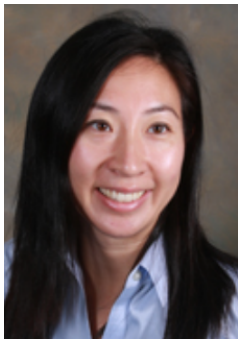
Optimal Treatment of Hormone Receptor Positive Disease



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Disclosures

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Speaker's Bureau:	**none**
Advisory Panel/Consultant:	**none**
Stock/Shareholder:	**none**
Employee:	**none**

Outline

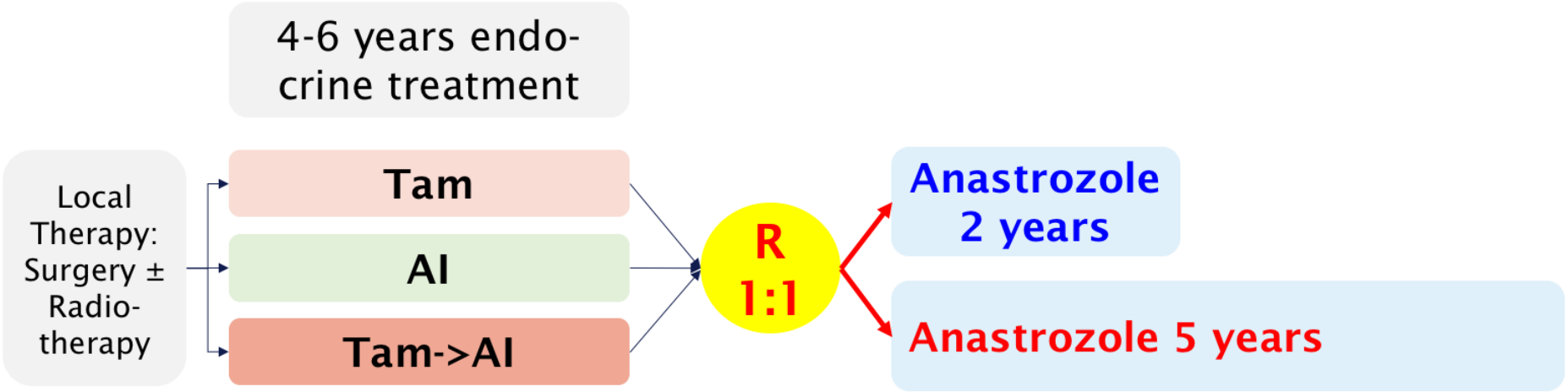
- Duration of adjuvant therapy
  - GS3-01 ABCSG 16: 7 vs 10 years adjuvant HT (Gnant et. al)
  - GS1-06 SUCCESS A: 2 vs 5 years adjuvant zoledronic acid (Janni et. al)
- Prognostic biomarkers for late recurrence
  - GS6-03 Circulating Tumor Cells (Sparano et. al)
  - GS6-01 CTS5 Clinical (Sestak et. al)
- GS4-02 and GS4-03 SOFT and TEXT update

A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial

Professor Michael Gnant, MD, FACS
Medical University of Vienna, Vienna, Austria

Michael Gnant, Guenther Steger, Richard Greil, Florian Fitzal, Brigitte Mlineritsch, Diether Manfreda, Christoph Tausch, Marija Balic, Peter Dubsky, Martin Moik, Josef Thaler, Daniel Egle, Vesna Bjelic-Radisic, Ursula Selim, Ruth Exner, Christian Singer, Elisabeth Melbinger-Zeinitzer, Ferdinand Haslbauer, Herbert Stoeger, Ruth Helfgott, Paul Sevelda, Harald Trapl, Viktor Wette, Lidija Soelkner, Raimund Jakesz, on behalf of the Austrian Breast and Colorectal Cancer Study Group

ABCSG-16 Trial Design



N=3,484

Postmenopausal, HR+, T1-3, N0/N+, M0

Recruitment in 75 centers in Austria, 2004-2010

Median Follow-Up: 106.2 months (102.7-107.7)

ABCSG-16 Patients (I)

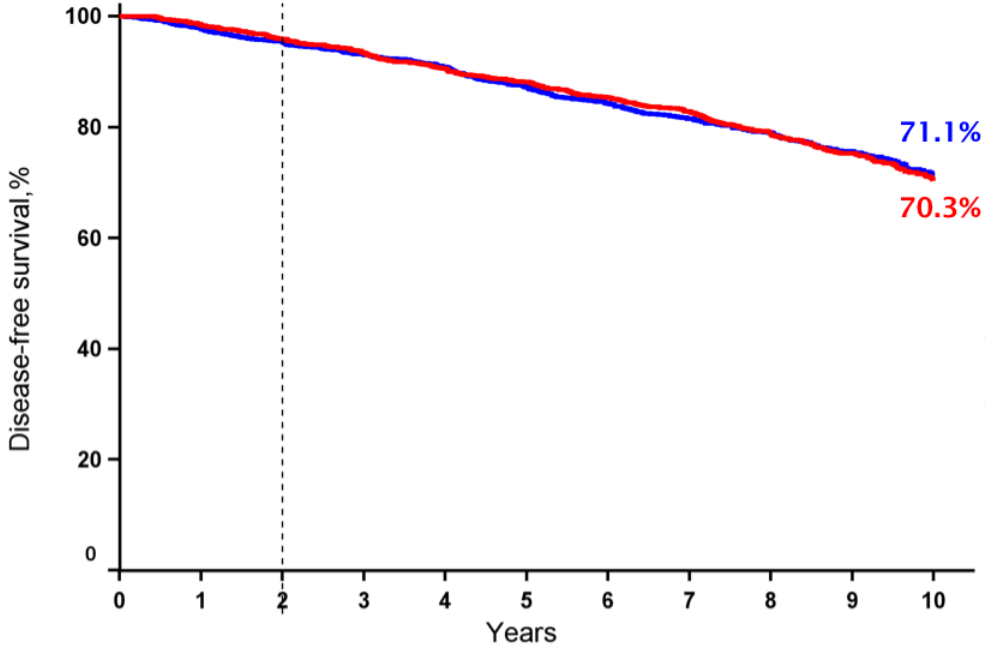
		2 Years Anastrozole N=1,731 n (%)	5 Years Anastrozole N=1,738 n (%)	Total N=3,469 n (%)
Median age	years (range)	65 (38-84)	64 (29-84)	64 (29-84)
pT-stage	pT1	1,253 (72.4)	1,254 (72.2)	2,507 (72.3)
	pT2/pT3/pTx	474 (27.4)	480 (27.6)	954 (27.5)
	Unknown	4 (0.2)	4 (0.2)	8 (0.2)
pN-stage	Negative	1,139 (65.8)	1,162 (66.9)	2,301 (66.3)
	Positive	551 (31.8)	523 (30.1)	1,074 (31.0)
	Unknown	4 (0.2)	4 (0.2)	8 (0.2)
Grading	G1	247 (14.3)	261 (15.0)	508 (14.6)
	G2/Gx	1,133 (65.5)	1,102 (63.4)	2,235 (64.4)
	G3	326 (18.8)	348 (20.0)	674 (19.4)
	Unknown	25 (1.4)	27 (1.6)	51 (1.5)
Hormone Receptor	ER+/PR+	1,354 (78.2)	1,330 (76.5)	2,684 (77.4)
	Any negative	375 (21.7)	401 (23.1)	776 (22.4)
	Unknown	2 (0.1)	7 (0.4)	9 (0.3)

ABCSG-16 Patients (II)

		2 Years Anastrozole N=1,731 n (%)	5 Years Anastrozole N=1,738 n (%)	Total N=3,469 n (%)
Type of surgery	Breast-conserving	1,360 (78.6)	1,406 (80.9)	2,766 (79.7)
	Mastectomy	370 (21.4)	329 (18.9)	699 (20.1)
	Unknown	1 (0.1)	3 (0.1)	4 (0.2)
Radiotherapy	yes	1,373 (79.3)	1,407 (81.0)	2,780 (80.1)
	no	355 (20.5)	327 (18.8)	682 (19.7)
	Unknown	3 (0.24)	4 (0.2)	7 (0.2)
Chemotherapy	Containing anthracycline	246 (14.2)	236 (13.6)	482 (13.9)
	Containing taxane	93 (5.4)	95 (5.5)	188 (5.4)
	Other chemotherapy	167 (9.6)	163 (9.4)	330 (9.5)
	No chemotherapy	1,223 (70.7)	1,241 (71.4)	2,464 (71.0)
	Unknown	2 (0.1)	3 (0.2)	5 (0.1)
Endocrine therapy in first 5 years	Tamoxifen	884 (51.1)	880 (50.6)	1,764 (50.9)
	Tamoxifen + AI	722 (41.7)	723 (41.6)	1,445 (41.6)
	AI	125 (7.2)	135 (7.8)	260 (7.5)

ABCSG-16 Disease-Free Survival

Time from randomization to first DFS event

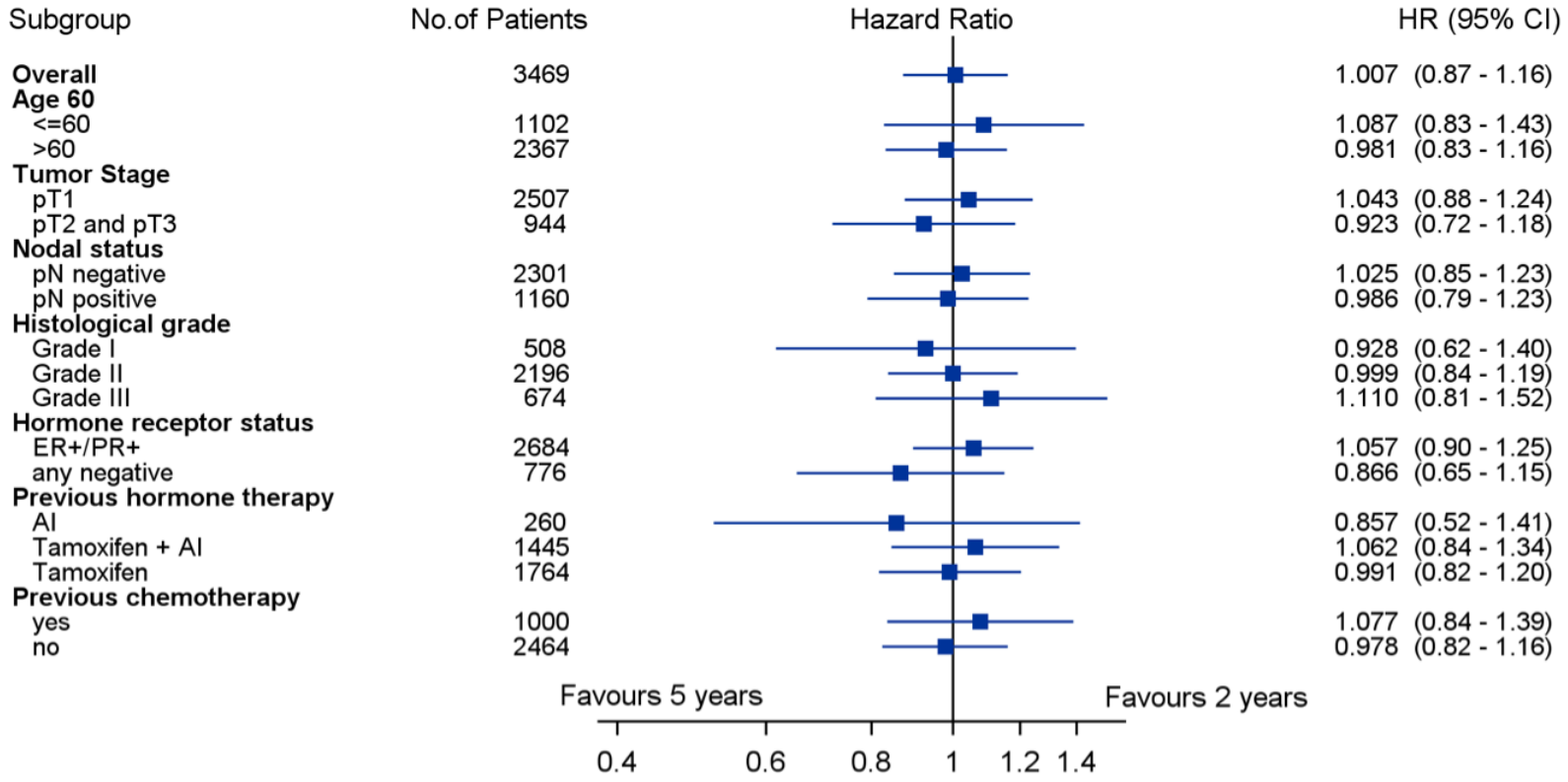


	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	378/1,731	1.007 (0.87, 1.16)	0.925
5 years	384/1,738		

Patients at risk:

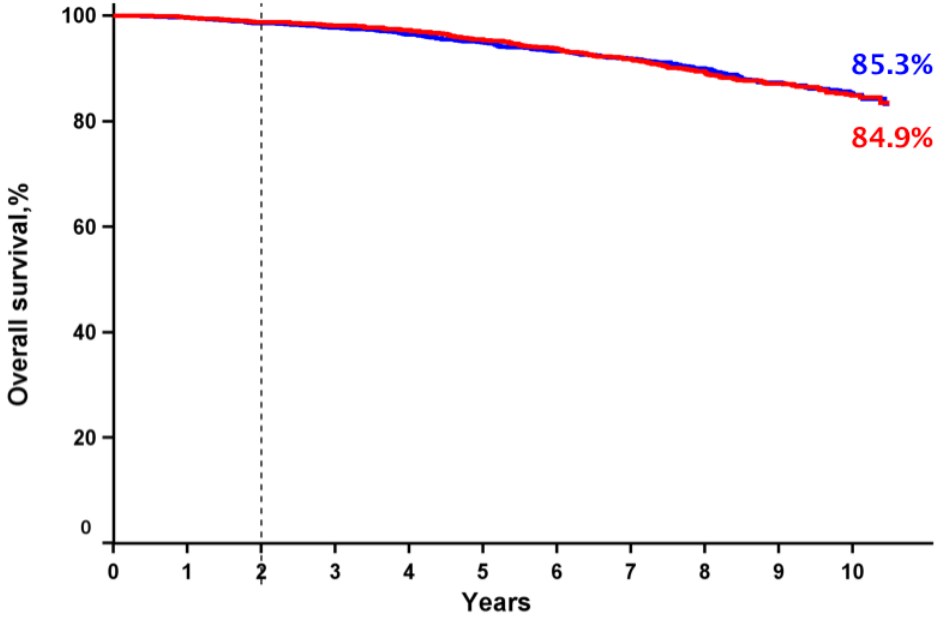
2 years	1731	1651	1601	1538	1477	1368	1206	990	741	540	214
5 years	1738	1667	1605	1551	1485	1399	1233	1026	779	554	209

ABCSG-16 DFS Subgroups



ABCSG-16 Secondary End Point: Overall Survival

Time from randomization to death from any cause



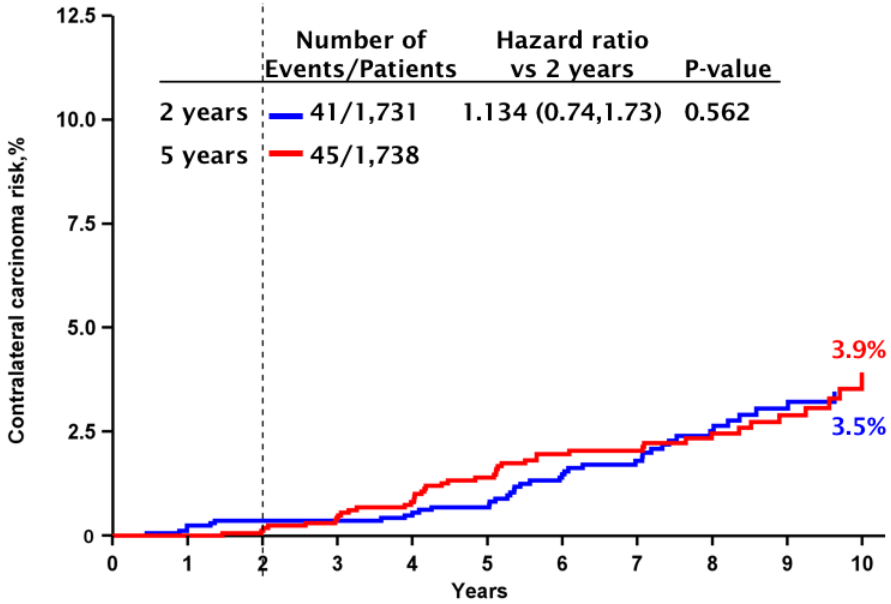
Patients at risk:

2 years	1731	1689	1661	1626	1594	1518	1352	1125	901	701	381
5 years	1738	1694	1659	1637	1606	1533	1362	1156	920	710	361

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	192/1,731	1.007 (0.82,1.23)	0.947
5 years	194/1,738		

ABCSG-16 Secondary End Points

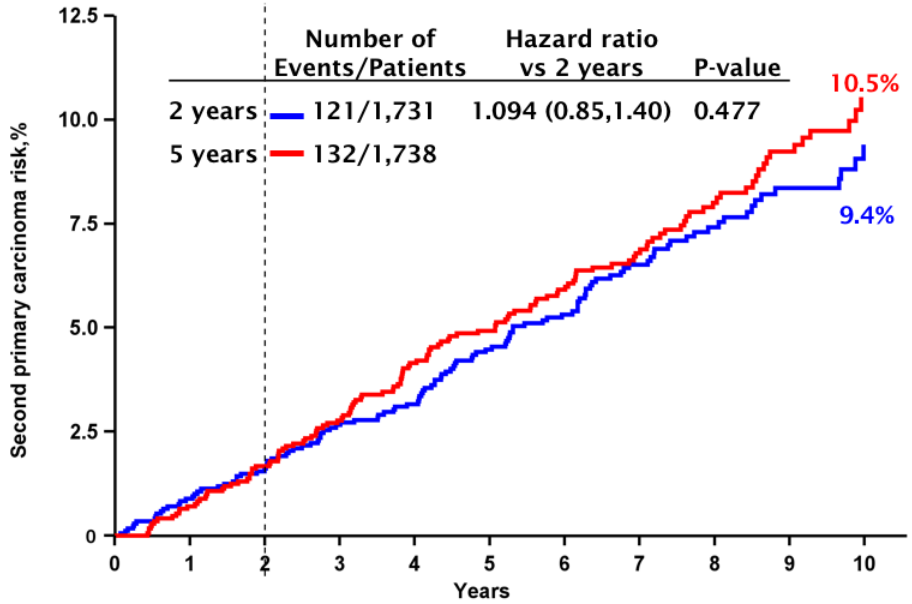
Contralateral Breast Cancer



Patients at risk:

2 years	1731	1662	1629	1585	1528	1448	1282	1058	794	588	252
5 years	1738	1676	1639	1602	1539	1454	1279	1065	821	599	235

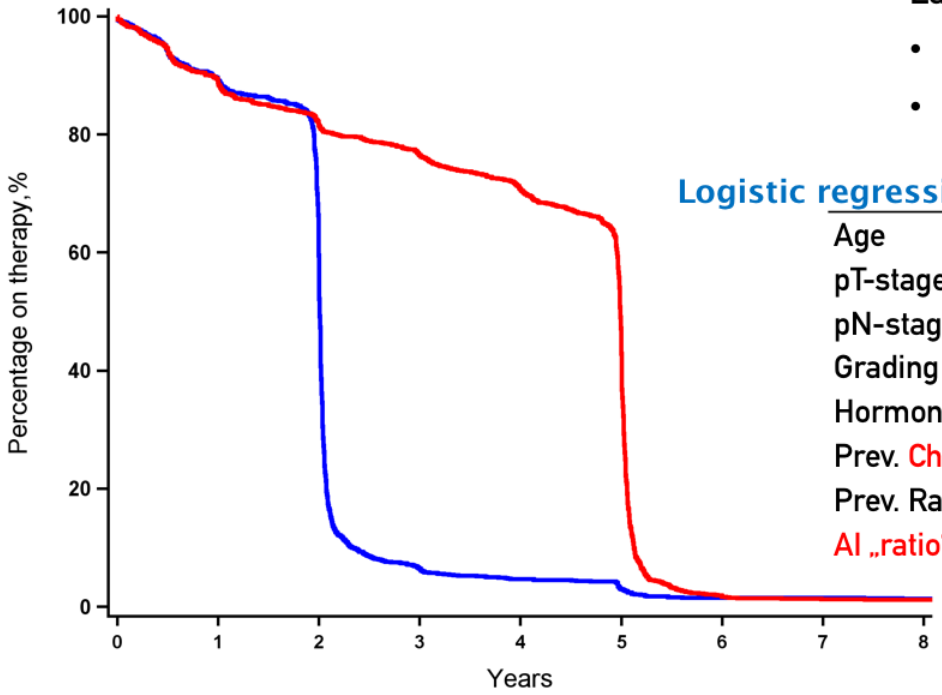
Secondary Primary Cancer



Patients at risk:

2 years	1731	1656	1616	1559	1502	1417	1261	1040	785	583	245
5 years	1738	1668	1618	1571	1502	1424	1253	1043	800	583	229

ABCSG-16 Treatment Adherence

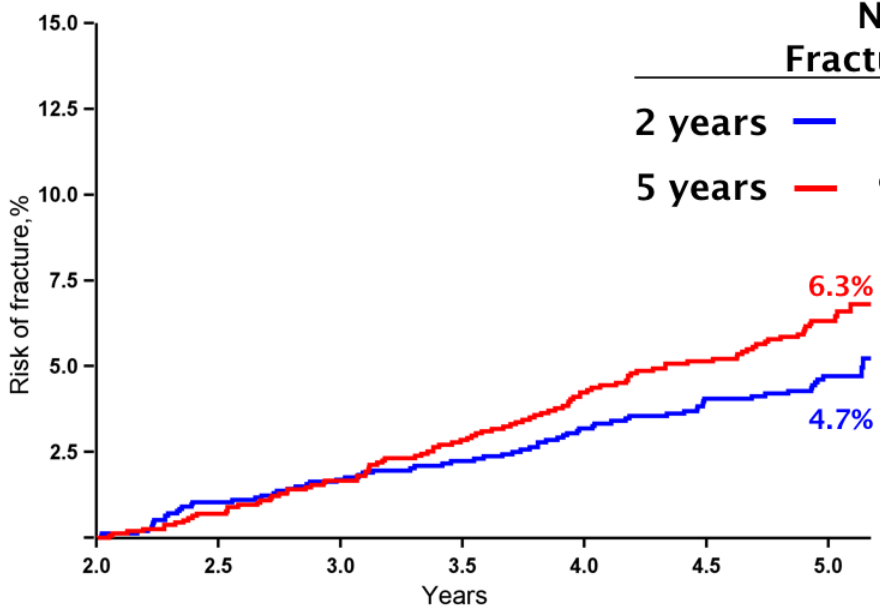


	2 years	5 years
Early/late EOT	421 (24.3%)	706 (40.6%)
• without event	356 (20.6%)	567 (32.6%)
• for DFS event	65 (3.8%)	139 (8.0%)

Logistic regression: Non-Adherent *vs* Adherent		Odds Ratio (95% CI)	P-value
Age	>60 vs ≤60	1.07 (0.89, 1.29)	0.4454
pT-stage	pT2/pT3 *vs* pT1/pTX	1.01 (0.83, 1.22)	0.9560
pN-stage	positive *vs* negative	0.93 (0.77, 1.12)	0.4187
Grading	G3 *vs* G1/G2/GX	1.21 (0.98, 1.51)	0.0806
Hormone Receptor	ER+/PR+ vs any neg.	0.91 (0.75, 1.10)	0.3190
Prev. Chemotherapy	yes *vs* no	0.79 (0.63, 0.98)	0.0303
Prev. Radiotherapy	yes *vs* no	1.10 (0.90, 1.35)	0.3660
AI „ratio“	continuous	0.65 (0.49, 0.86)	0.0030

Adherent patients:
all patients on treatment for 5 (±0.5) years in 5-years arm
all patients on treatment for 2 (±0.5) years in 2-years arm
all patients with DFS event during their treatment phase

ABCSG-16 Fractures



	Number of Fractures/Patients	Hazard ratio vs 2 years	P-value
2 years	71/1,556	1.353 (1.00,1.84)	0.053
5 years	98/1,571		

Patients at risk:

2 years	1556	1515	1480	1439	1386	1313	843
5 years	1571	1549	1514	1477	1416	1347	857

ABCSG-16 Summary

- In postmenopausal hormone-receptor positive breast cancer patients receiving 5 years of standard adjuvant endocrine therapy (Tamoxifen, Aromatase Inhibitor, sequence), additional 5 years of Anastrozole **did not improve disease-free survival** as compared to additional 2 years of Anastrozole.
- ABCSG-16 did not show a difference between additional 2 years versus additional 5 years of Anastrozole in terms of secondary end points
  - Overall survival (OS)
  - Time to contralateral breast cancer
  - Time to second primary cancer
- There were **more fractures** in the study arm of 5 additional years of Anastrozole.

Extended AI Therapy Trials

	Prior Tx	Randomization	Node +	Prior Chemo	DFS/HR	P value
NSABP B-42	T → AI or 5 AI	AI x 5 vs Placebo	42%		84.7 (5 yrs) vs 81.3 HR 0.85 (.73-.999) 1.9% benefit in DR	0.048 NS (0.03 for DR)
IDEAL	T → AI T x 5 AI x 5	AI x 5 vs. AI x 2.5	74%	68%	87.9 vs 88.4 HR 0.96 (0.76-1.2)	0.7
DATA	T x 2-3	AI x 3 vs AI x 6	67%	70%	83.6 vs 79.4 HR 0.79 (0.62-1.02)	0.07
ABCSG 16	T → AI T x 5 AI x 5	AI x 2 vs AI x 5	31%	30%	71% vs 70% HR 1.007	0.925

Take-home: Optimal duration of hormone therapy

- Benefit of extended HT has only been demonstrated in the following settings:
  - TAM x 5 → TAM x 5 (aTTom, ATLAS)
  - TAM x5 → AI x 5 (MA 17, NSABP B-33, ABCSG 6a)
  - TAM x 5 → AIx5 → AI x 5 (MA 17.R) – lower risk of new primary/contralateral BC
- No study has yet showed benefit of extended AI therapy after AI therapy during first 5 years
- Trends for benefit in some higher risk subsets but currently no reliable way to predict who may benefit
- Increased rates of fracture, new onset osteoporosis, endometrial cancer
- Must individualize treatment considering underlying risk and short/long term side effects

Extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: Phase III data from the SUCCESS A study

Wolfgang Janni, Thomas WP Friedl, Tanja Fehm, Volkmar Mueller, Werner Lichtenegger, Jens Blohmer, Ralf Lorenz, Helmut Forstbauer, Emanuel Bauer, Visnja Fink, Inga Bekes, Jens Huober, Julia Jückstock, Andreas Schneeweiss, Hans Tesch, Sven Mahner, Sara Y Brucker, Georg Heinrich, Lothar Häberle, Peter A. Fasching, Matthias W Beckmann, Robert Coleman, Brigitte Rack

SUCCESS A – study design

(open-label, multicenter, 2x2 factorial design, randomized controlled Phase III study)

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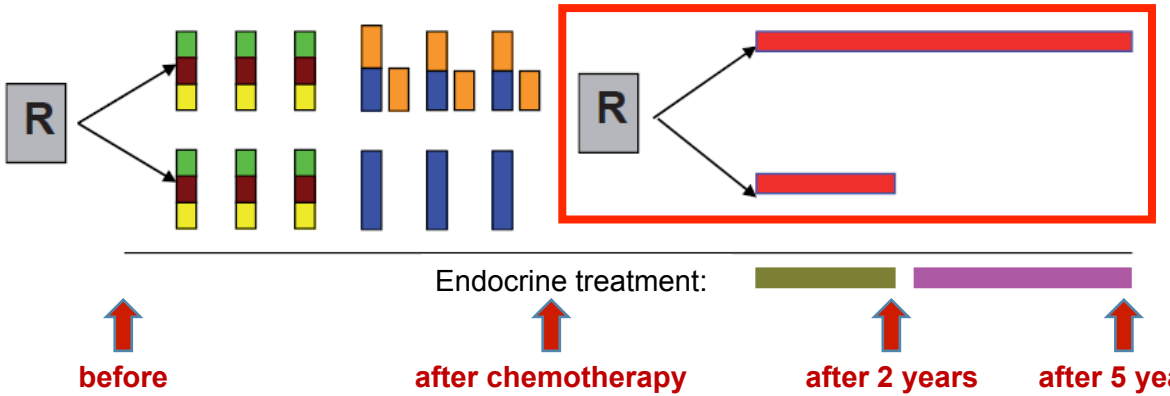

5- FU 500 mg/m², Epirubicin 100 mg/ m², Cyclophosphamide 500 mg/m² q3w

Docetaxel 100 mg/m² q3w

Docetaxel 75 mg/m², Gemcitabine 1.000 mg/m² d1,8 q3w

Tamoxifen 20 mg qid p.o. x 2a (plus Goserelin 3.6 mg depot x 2a in premenopausal pts

Anastrozole 1 mg qid p.o. x 3a in postmenopausal pts (Tam in premenopausal pts)

First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

Second randomization:
5 years vs. 2 years of zoledronate
(4 mg i.v. every 3 months for 2 years, followed by 4 mg i.v. every 6 months for 3 years vs. 4 mg i.v. every 3 months for 2 years)

Patient characteristics (n = 2987)

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Patient and tumor characteristics*		5 years of zoledronate		2 years of zoledronate	
		n	%	n	%
Tumor size	*pT1/pT2*	1451	94.2	1351	93.4
	pT3/pT4	86	5.6	95	6.6
Nodal stage	*pN0*	516	33.5	520	35.9
	pN+	1018	66.1	924	63.9
Histological grading	*G1*	82	5.3	68	4.7
	G2	752	48.8	707	48.9
	G3	705	45.8	672	46.4
Histological type	*ductal*	1280	83.1	1181	81.6
	other	258	16.8	266	18.4
Hormone receptor status	*negative*	406	26.4	422	29.2
	positive	1132	73.5	1024	70.8
HER2 status	*negative*	1151	74.7	1083	74.8
	positive	357	23.2	341	23.6
Menopausal status	*premenopausal*	649	42.1	614	42.4
	postmenopausal	891	57.9	833	57.6
Type of surgery	*breast conserving*	1090	70.8	1054	72.8
	mastectomy	449	29.2	393	27.2
Adjuvant chemotherapy	*FEC-DocG*	744	48.3	732	50.6
	FEC-Doc	796	51.7	715	49.4

Patients in the two randomization arms well balanced with regard to clinicopathological characteristics (all $p > 0.05$)

* missing data in some categories

Adapted disease-free survival (DFS) and overall survival (OS) by zoledronate treatment arm

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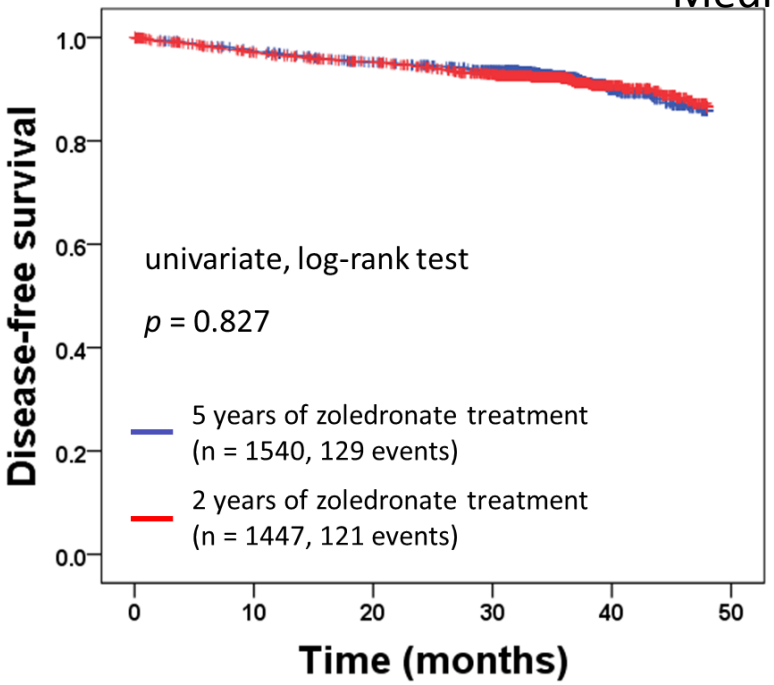
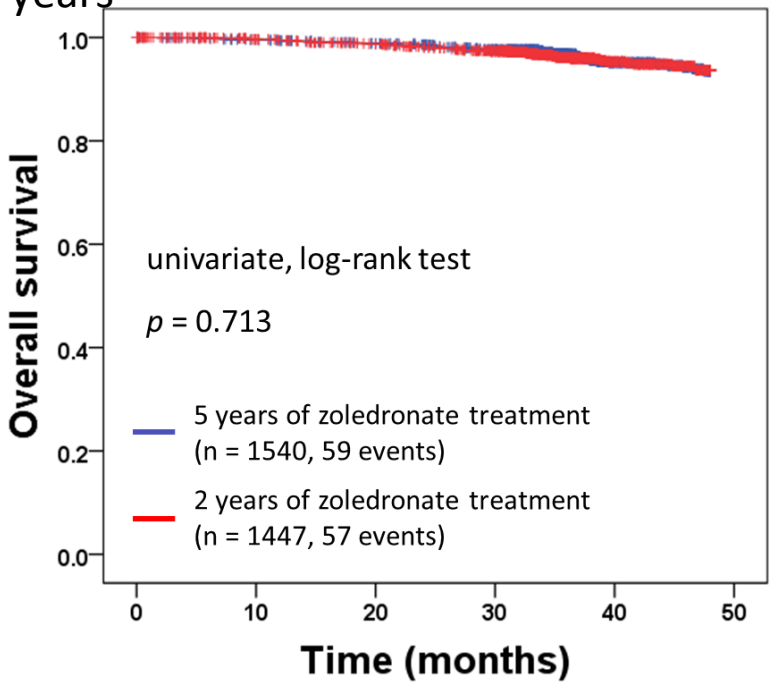
Median f/u <3 years





Subgroups – adapted DFS by menopausal status

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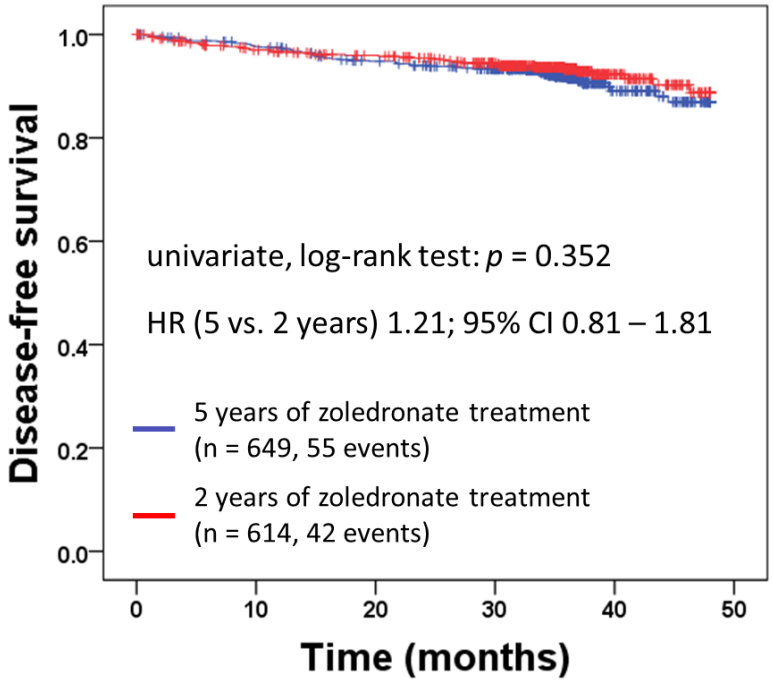
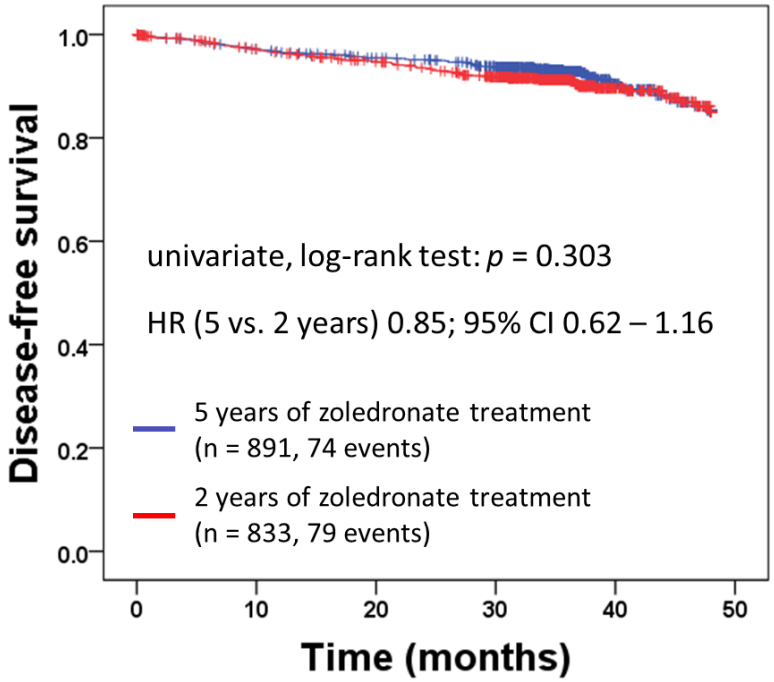
premenopausal



postmenopausal



Subgroups – adapted OS by menopausal status

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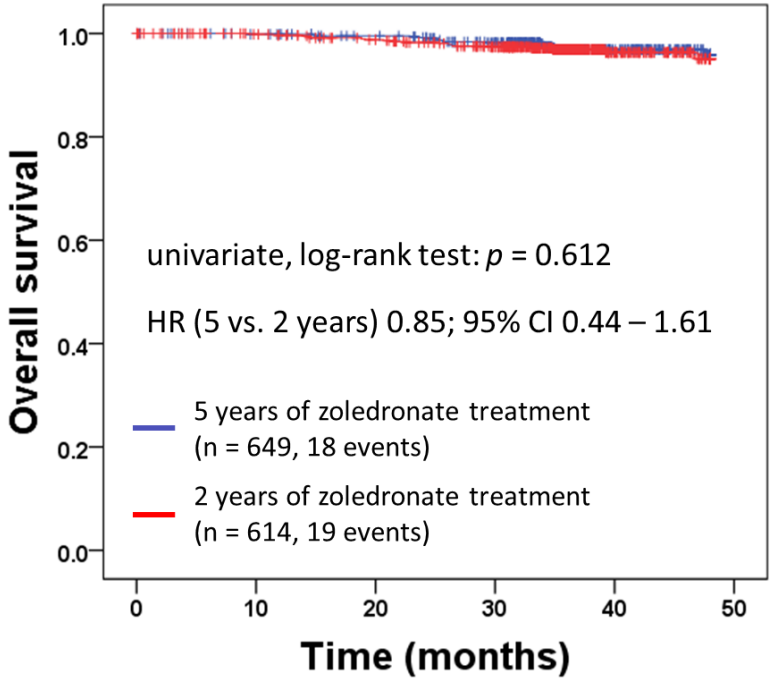
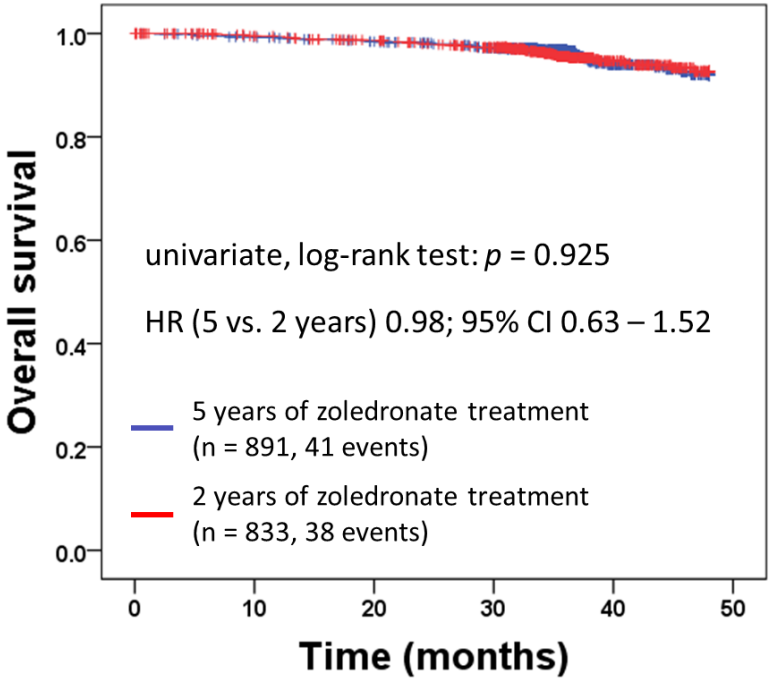
premenopausal



postmenopausal



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Observed frequency (% of patients affected) of 10 most common adverse events

Adverse event	5 years of zoledronate		2 years of zoledronate	
	all grades	grade 3/4	all grades	grade 3/4
Bone pain	158 (8.3%)	9 (0.6%)	57 (3.7%)	5 (0.3%)
Arthralgia	96 (5.1%)	1 (0.1%)	50 (3.1%)	1 (0.1%)
Fatigue	78 (4.4%)	5 (0.3%)	34 (2.1%)	0 (0.0%)
Anemia	84 (4.4%)	1 (0.1%)	7 (0.5%)	1 (0.1%)
Neuropathy	47 (2.3%)	0 (0.0%)	32 (1.9%)	2 (0.1%)
Leukopenia	63 (3.6%)	0 (0.0%)	8 (0.6%)	3 (0.2%)
Hot flashes	41 (2.2%)	0 (0.0%)	25 (1.5%)	0 (0.0%)
Myalgia	39 (2.1%)	4 (0.3%)	17 (1.1%)	0 (0.0%)
SGPT (serum glutamic pyruvic transaminase) elevation	42 (2.5%)	1 (0.1%)	12 (0.7%)	0 (0.0%)
Headache	33 (1.8%)	4 (0.3%)	21 (1.2%)	0 (0.0%)

Osteonecrosis of the jaw (ONJ) occured in 11 cases vs. 5 cases (5y vs 2y)

Take-home: duration of bisphosphonates

- Optimal duration and schedule of adjuvant zoledronic acid is not clear
  - ABCSG-12: q6 month x 3 years
  - AZURE : Q3-4wks x 6 →q3-6months for total 5 years
  - ZO-FAST: q6months x 5 years
- Cancer Care Ontario and ASCO Clinical Practice Guidelines (Dhesy-Thind et al. JCO 2017) recommends 3-5 years.
- SUCCESS A showed no significant benefit in DFS or OS between patients receiving 2 vs 5 years of adjuvant zolderonic acid
  - Short f/u (3 years), few events
  - benefit delayed
  - 2 year arm received q3 months infusions
- Recommend at least 3 years zoledronic acid. Consider underlying risk, bone density, risk for ONJ when determining need and duration.

40th Annual San Antonio Breast Cancer Symposium, December 5-9, 2017

Circulating Tumor Cells and Late Recurrence of Breast Cancer

Joseph A. Sparano, MD[1], Anne O'Neill, MS[2], Katherine Alpaugh, PhD[3], Antonio C. Wolff, MD[4], Donald W. Northfelt, MD[5], Chau T. Dang, MD[6], George W. Sledge, MD[7], Kathy Miller, MD[8]

1. Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; 2. Dana Farber Cancer Institute, Boston, MA; 3. Fox Chase Cancer Center, Philadelphia, PA; 4. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; 5. Mayo Clinic, Scottsdale, AZ; 6.Memorial Sloan Kettering Cancer Center, New York, NY; 7. Stanford Cancer Center, Palo Alto, CA; 8. Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

ECOG-ACRIN
cancer research group

Reshaping the future of patient care

Methods: Hypothesis & Study Objectives

Hypothesis:

CTCs are prognostic for late recurrence

Study Objectives:

1. **Prevalence of CTCs ~ 5 years after diagnosis**
2. **Association between CTCs and recurrence**

Methods: Study Design

- **Population:** Stage II-III HER2-negative enrolled in E5103 (NCT00433511)
- **Treatment:** AC-weekly paclitaxel ± bevacizumab + endocrine therapy if ER+
- **Selection:** Recurrence-free 4.5-7.5 years after diagnosis & informed consent
- **CTC Assay:** Whole blood (7.5 ml) drawn into fixative-containing tube for CTC identification and enumeration using the CellSearch® system at entry
- **Assay results:** not reported to clinicians or patients due to uncertainty regarding prognostic information

Results: Patient Characteristics, Recurrences, & CTC Results

(Enrollment Period: February 2013 – July 2016)

Total	Total (N=547)
Age at diagnosis (n=547)	
< 50 years	44%
>= 50 years	56%
Tumor size (N=547)	
< 2 cm	41%
>/= 2 cm	59%
Nodal Status	
Negative	27%
Positive	73%
HR Expression (N=546)	
Negative	35%
Positive	65%
Histologic grade (N-534)	
Low-intermediate	45%
High	55%
Endocrine Therapy (N=330)	88%

- **Median followup – 1.8 years**
  - Range 0-3.9 years
- **Recurrences**
  - **HR-Positive (N=14/353): 4.0%** (95% CI 3.0 to 7.9%) – DISTANT
  - **HR-Negative (N=1/193): 0.5%** (95% CI 0, 2.9%) - LRR

- **CTC-Positive (1 cell/7.5 ml blood)**
  - **Overall (N=26): 4.8%** 95% CI 3.1%-6.9%
  - **HR-Positive (N=18/353): 5.1%** 95% CI 3.0%-7.9%
  - **HR-Negative (N=8/193): 4.1%** 95% CI 1.8%-9.0%

Results: Patient Characteristics

Total	CTC+ (N=26)	CTC- (N=521)
Age at diagnosis (n=547)		
< 50 years	54%	44%
>= 50 years	46%	56%
Tumor size (N=547)		
< 2 cm	38%	41%
>/= 2 cm	62%	59%
Nodal Status (N=547)		
Negative	19%	28%
Positive	81%	72%
HR Expression (N=546)		
Negative	31%	36%
Positive	69%	64%
Histologic grade (N-534)		
Low-intermediate	54%	45%
High	46%	55%
Endocrine Therapy (N=330)	88%	87%

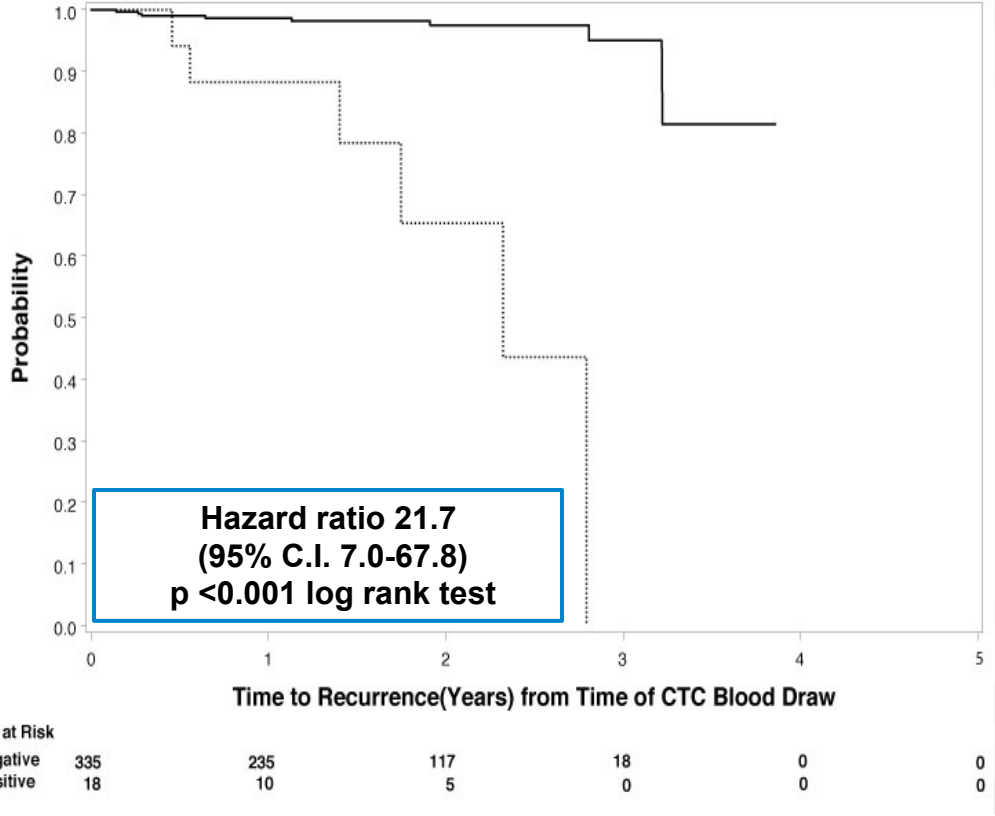
No Significant Difference in Characteristics of CTC-Positive vs. CTC-Negative

Results: Time to Recurrence in HR+ Disease (N=353)

Median time to recurrence in CTC+: 1.6 years (range 0.5-2.8 years)

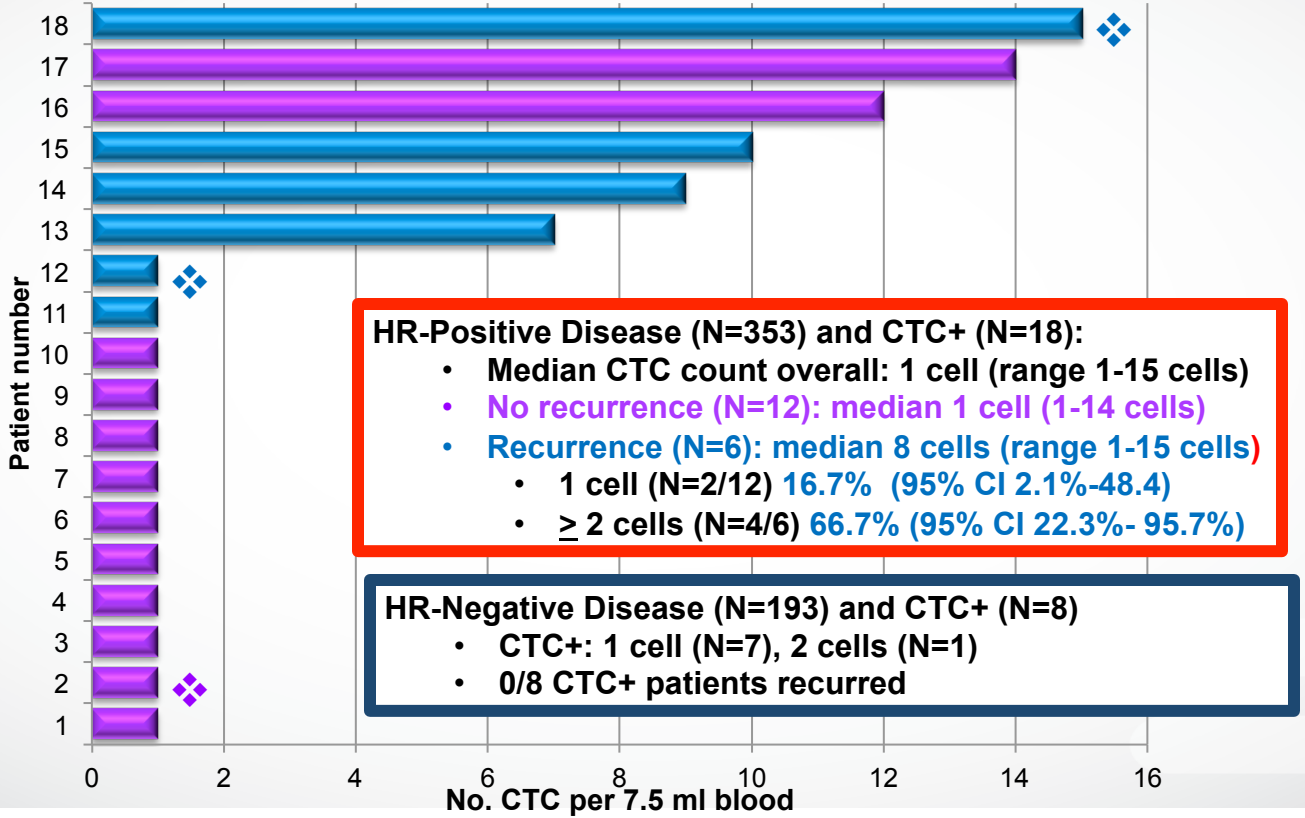
2-Year Recurrence

- Positive Predictive Value = 35%
- Negative Predictive Value = 98%



Results: CTC Burden & Recurrence in HR+ Disease (N=18)

(all taking endocrine therapy except 3 patients denoted by symbol ❖)



HR-Positive Disease (N=353) and CTC+ (N=18):

- Median CTC count overall: 1 cell (range 1-15 cells)
- No recurrence (N=12): median 1 cell (1-14 cells)
- Recurrence (N=6): median 8 cells (range 1-15 cells)
  - 1 cell (N=2/12) 16.7% (95% CI 2.1%-48.4)
  - ≥ 2 cells (N=4/6) 66.7% (95% CI 22.3%- 95.7%)

HR-Negative Disease (N=193) and CTC+ (N=8)

- CTC+: 1 cell (N=7), 2 cells (N=1)
- 0/8 CTC+ patients recurred

Conclusions

- CTCs detectable in 5% of patients with localized HR+, HER2- breast cancer 5 years or more after diagnosis
- Also detected in 4% of HR-, HER- ("triple-negative") disease
- Authors found a 21 fold higher risk of late recurrence in patients with +CTC in HR+ patients only

Discussion: Strengths and Limitations

- **Strengths**
  - **Prospective study in high risk patients**
  - **Clinicians blinded to CTC result**
- **Limitations**
  - **Positive CTC did not trigger imaging studies – Did the +CTC patients already have metastatic disease?**
  - **Why no association with recurrence in ER-negative disease?**
  - **Median followup of 1.8 years is relatively short for ER+ disease**

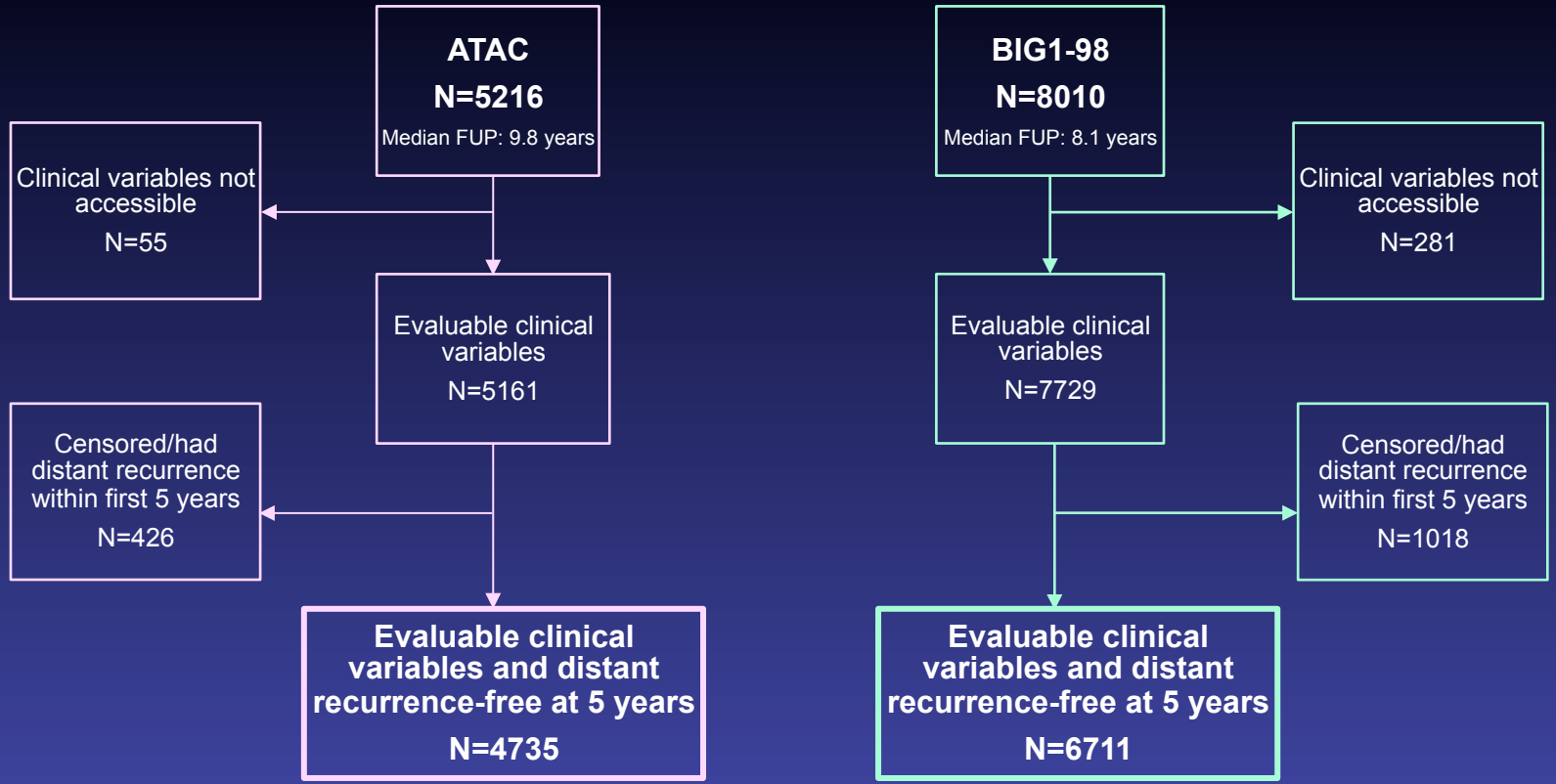
Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor positive breast cancer treated with 5 years of endocrine therapy

Ivana Sestak[1]

Meredith M. Regan[2], Andrew Dodson[3], Giuseppe Viale[4], Beat Thürlimann[5], Marco Colleoni[6], Jack Cuzick[1], Mitch Dowsett[3]

1. Centre for Cancer Prevention, Queen Mary University of London, London, United Kingdom
2. Dana Farber Cancer Institute, Boston, United States
3. Ralph Lauren Centre for Breast Cancer Research, Royal Marsden, London, United Kingdom
4. European Institute of Oncology & University of Milan, Milan, Italy
5. Kantonsspital St. Gallen, St. Gallen, Switzerland
6. European Institute of Oncology, Milan, Italy

Training/validation cohorts



Patient characteristics

	ATAC (N=4735)	BIG 1-98 (N=6711)
Age (years), median (IQR)	64 (57-71)	61 (56-67)
Nodal involvement		
Negative	68.0%	60.9%
1-3	24.6%	29.0%
4+	7.4%	10.1%
Grade		
Well	24.3%	22.7%
Intermediate	50.4%	57.0%
Poor	25.3%	20.3%
Tumour size		
<10mm	19.7%	17.5%
10-20mm	49.8%	47.8%
>20mm	32.0%	34.8%
Chemotherapy	19.5%	24.2%
Endocrine therapy		
Tamoxifen 5 years	50.1%	29.6%
Anastrozole or Letrozole 5 years	49.9%	30.4%
2 years Letrozole/3 Years Tamoxifen	-	19.9%
2 years Tamoxifen/3 Years Letrozole	-	20.0%
Distant recurrence (>5 years)	**7.0%**	**5.5%**

CTS5 score development

- Univariate Cox regression to determine prognostic value of each variable:

Clinical variable	HR (95% CI)	P-value
Number of positive nodes	1.14 (1.12-1.15)	<0.0001
Tumor size (mm)	1.10 (1.08-1.12)	<0.0001
Grade (1 vs. 2, 1 vs. 3)	2.26 (1.58-3.22) / 3.37 (2.33-4.86)	<0.0001 / <0.0001
Age (years)	1.04 (1.02-1.05)	<0.0001
Endocrine therapy (T vs. A)	0.84 (0.67-1.04)	0.108

Final CTS5 model:

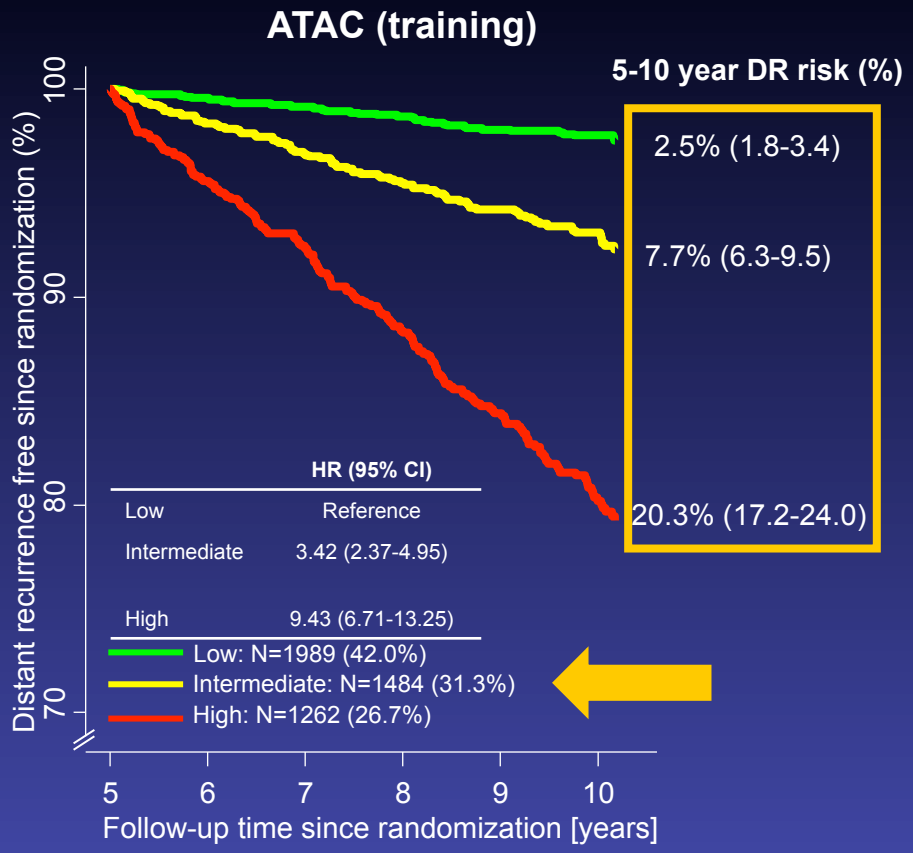
Node:
0 = Negative
1 = 1 positive
2 = 2-3 positive
3 = 4-9 positive
4 = >9 positive

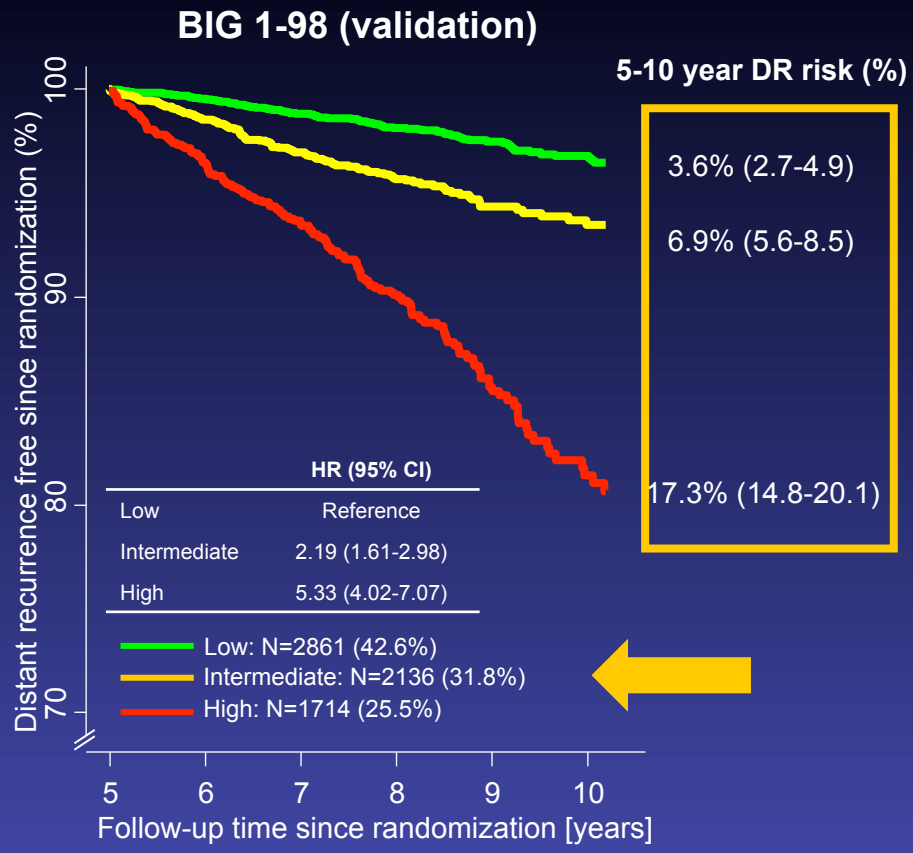
Size:
Continuous
(if >30 then = 30)

Grade:
0 = Grade 1
1 = Grade 2
2 = Grade 3

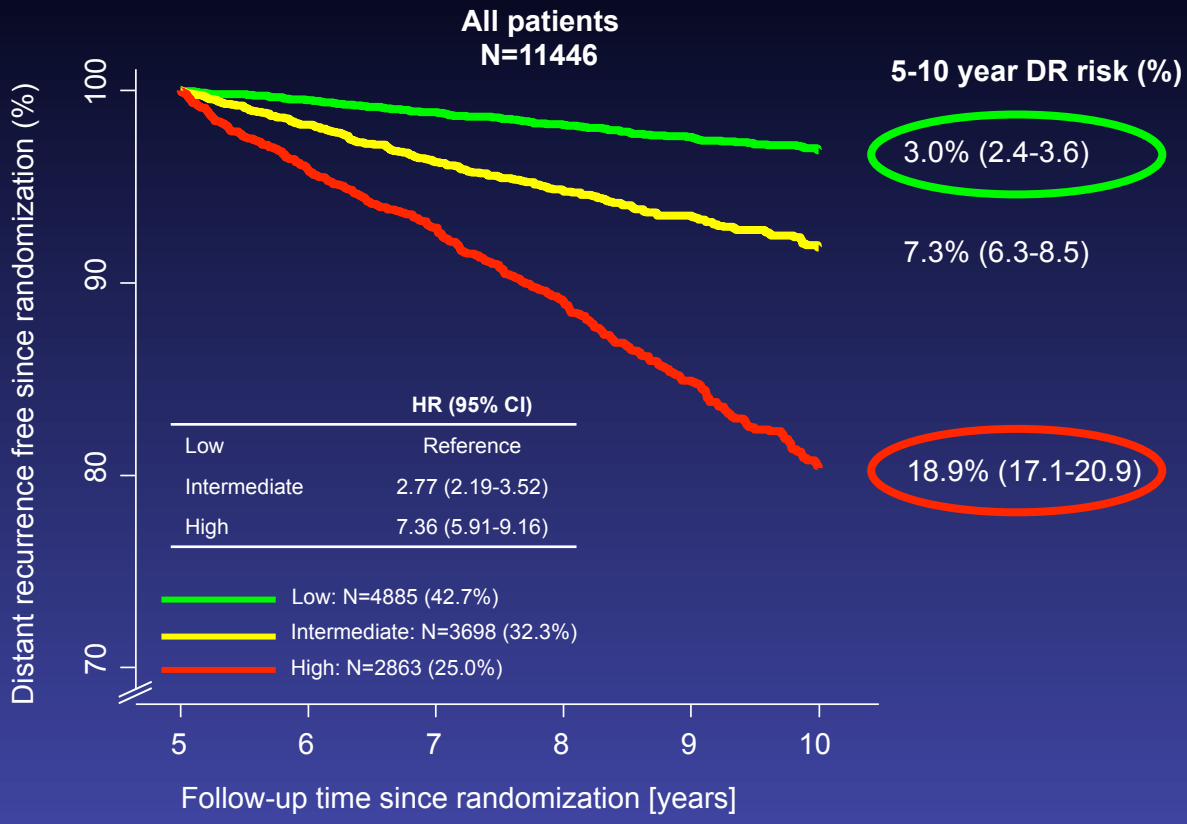
Age:
Continuous

DR free (%) in years 5-10

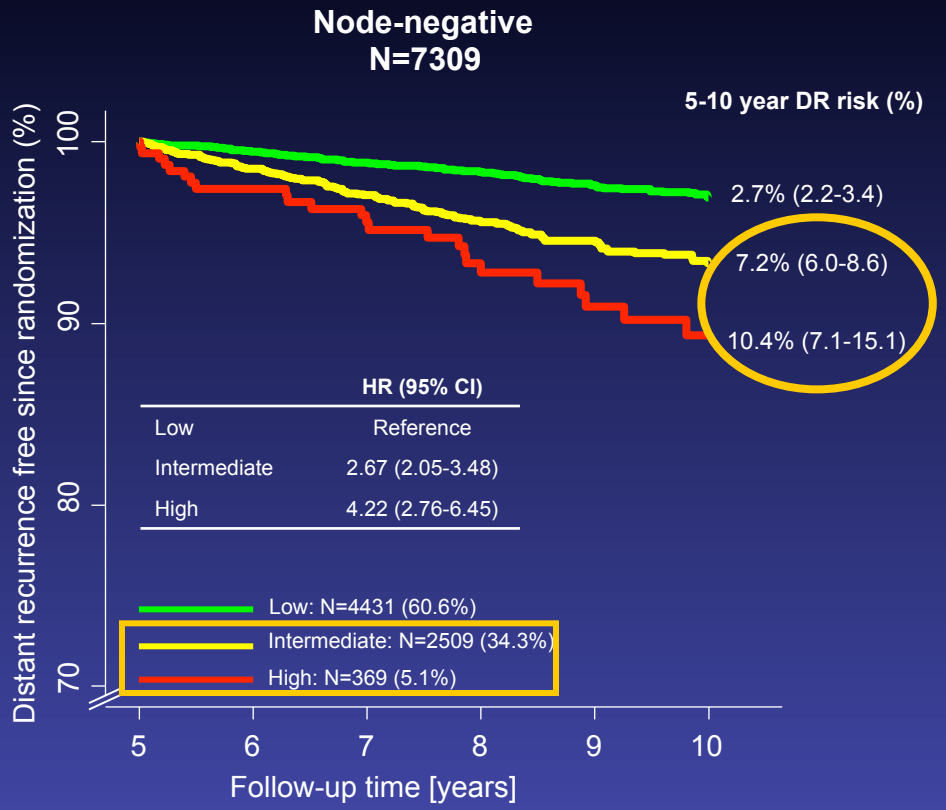




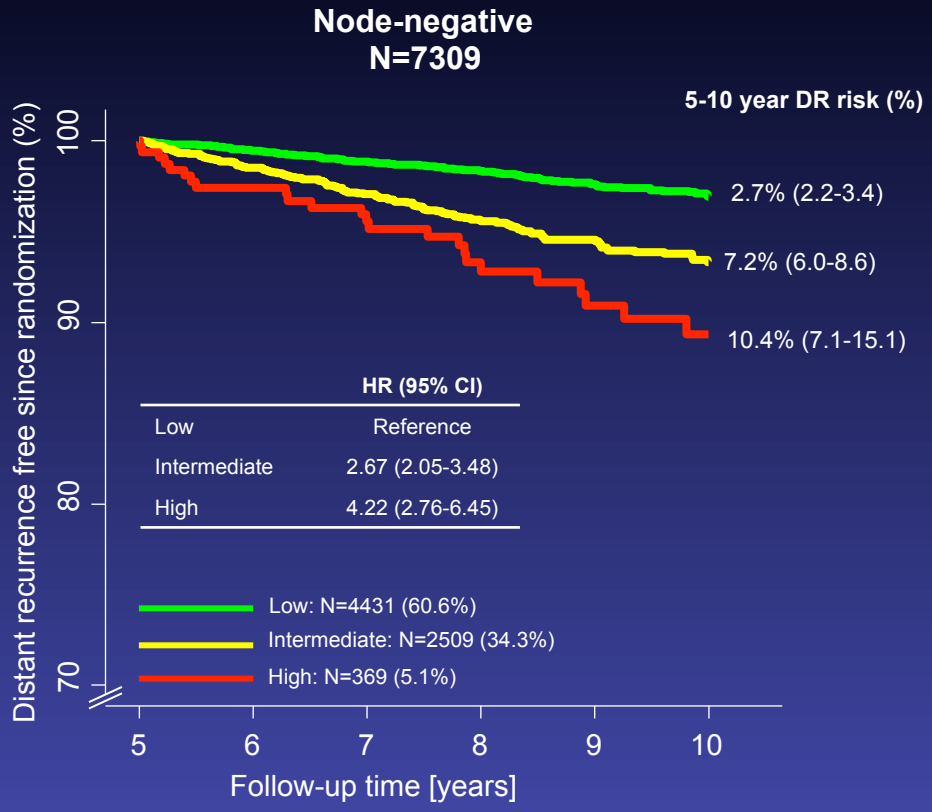
Combined dataset: DR free (%)

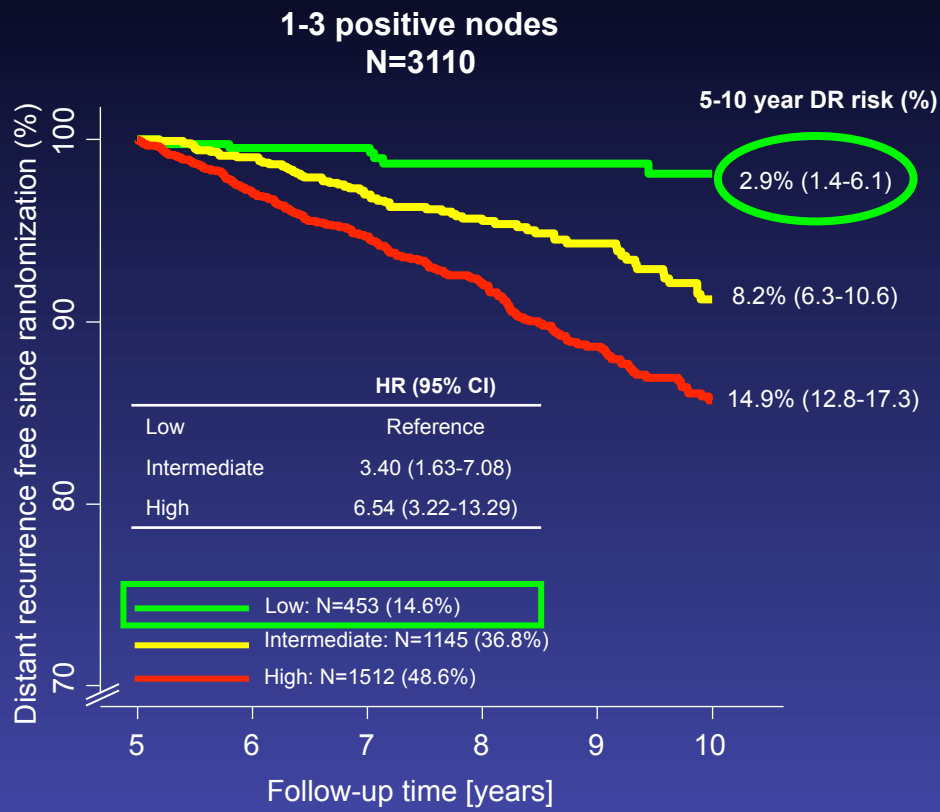


Combined dataset: DR free (%)



Combined dataset: DR free (%)





Summary

- CTS5 was prognostic for development of late DR
- Strengths :
  - large data sets with long-term follow up and comprehensive clinicopathologic data
- Limitations:
  - Only postmenopausal women
  - HER2 unknown
  - Is CTS5 better than nodal status alone?

Take home: late recurrence

- >50% recurrences occur after 5 years
- Predicting who is at risk of a late recurrence is a critical unmet clinical need
- Clinicopathologic factors (ie. LN status) are useful and several biomarkers are actively being developed to address this need (ie. BCI, Prosigna, EndoPredict)
- Currently insufficient data to recommend routine use of any test to select patients for extended therapy
- Efforts to test biomarkers in extended AI trials are planned

Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with HR+ Early Breast Cancer: Update Of The Combined TEXT and SOFT Trials

Prudence Francis

on behalf of Olivia Pagani, MD

TEXT and SOFT Investigators and

International Breast Cancer Study Group (IBCSG)

TEXT and SOFT Designs

Enrolled: Nov03-Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo *OR* planned chemo

RANDOMIZE

TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)
TEXT

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo

OR

- Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE

SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)
SOFT

- Tamoxifen x 5y
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Joint Analysis (N=4690)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

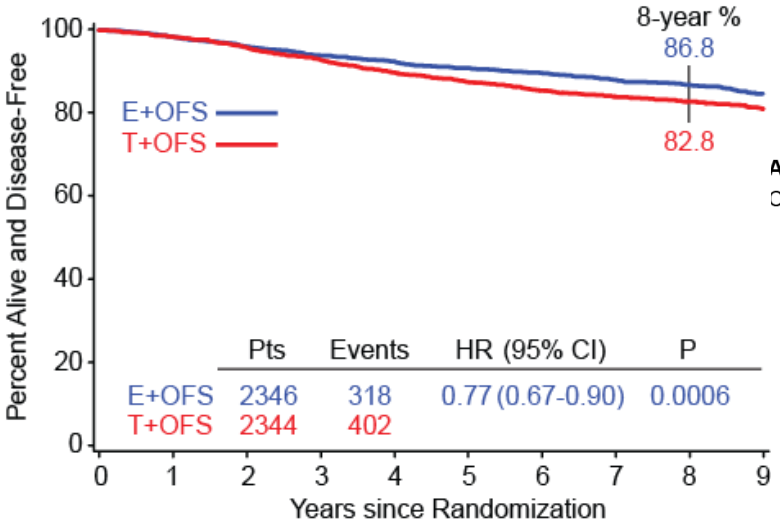
Median follow-up 9 years

OFS=ovarian function suppression

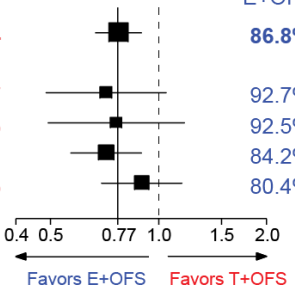
Patient Characteristics

	No chemo TEXT (N=1053)	No chemo SOFT (N=943)	Chemo TEXT (N=1607)	Prior chemo SOFT (N=1087)	Overall (N=4690)
Age <40 yr	16%	9%	30%	49%	27%
LN +	21%	8%	66%	57%	42%
T-size >2cm	19%	15%	53%	47%	36%
HER2 +	5%	3%	17%	20%	12%
Surgery to random. (median)	1.5 mo	1.8 mo	1.2 mo	8.0 mo	1.6 mo

Sustained Improvement in DFS



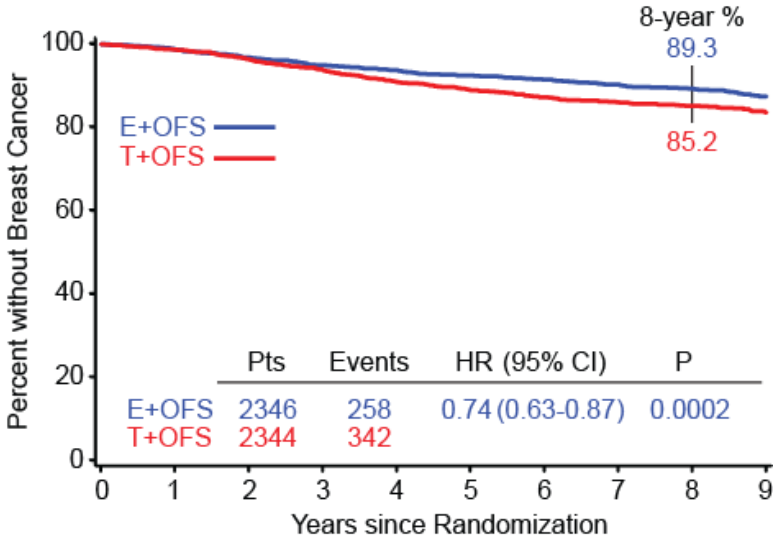
	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DFS E+OFS	8-Year DFS T+OFS	Difference
All Patients	**318**	**2346**	**402**	**2344**	**86.8%**	**82.8%**	**+ 4.0%**
Cohort							
No Chemotherapy TEXT	44	526	62	527	92.7%	89.1%	+ 3.6%
No Chemotherapy SOFT	35	470	47	473	92.5%	90.6%	+ 1.9%
Chemotherapy TEXT	131	806	173	801	84.2%	78.2%	+ 6.0%
Prior Chemotherapy SOFT	108	544	120	543	80.4%	76.7%	+ 3.7%



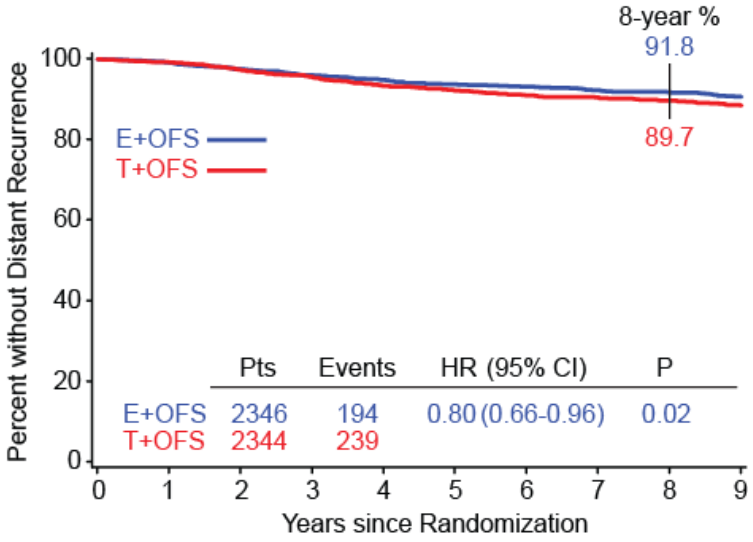
4.0% absolute improvement in 8-yr DFS for E+OFS after 9 years median follow-up

Significant Reductions in Recurrence

Breast Cancer-Free Interval



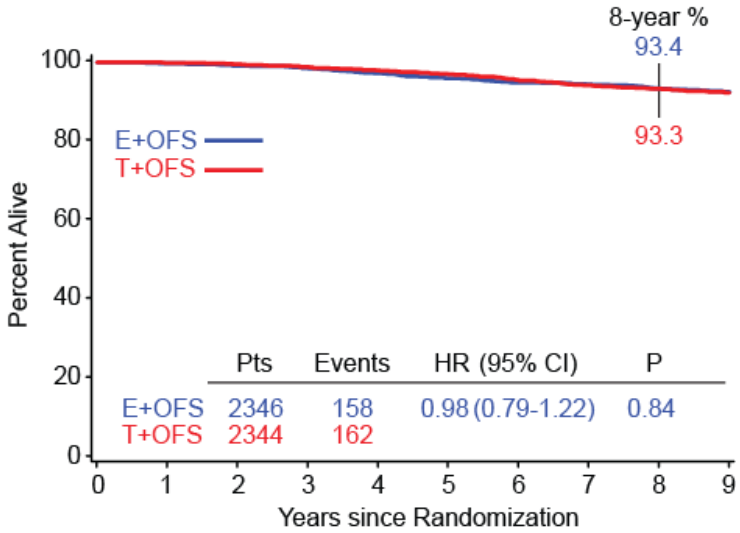
Distant Recurrence-Free Interval



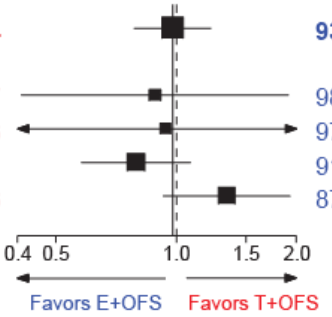
4.1% absolute improvement in 8-yr freedom from breast cancer for E+OFS

2.1% absolute improvement in 8-yr freedom from distant recurrence for E+OFS

Overall Survival



	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year OS E+OFS	8-Year OS T+OFS
All Patients	**158**	**2346**	**162**	**2344**	**93.4%**	**93.3%**
Cohort						
No Chemotherapy TEXT	12	526	14	527	98.4%	98.1%
No Chemotherapy SOFT	9	470	10	473	97.7%	97.9%
Chemotherapy TEXT	70	806	87	801	91.7%	90.1%
Prior Chemotherapy SOFT	67	544	51	543	87.2%	89.4%

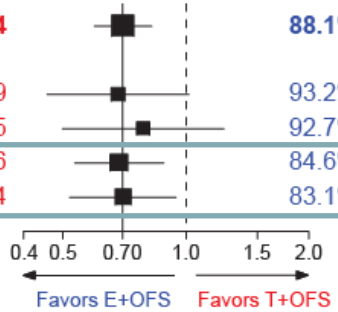


E+OFS did not improve Overall Survival vs T+OFS, after 9 years median follow-up

HER2-negative Patients (N=4035)

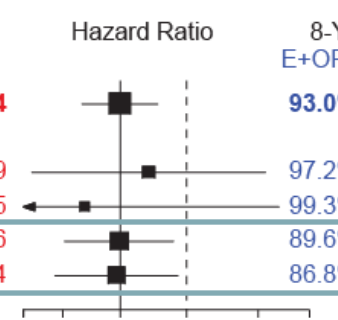
DFS

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DFS E+OFS	8-Year DFS T+OFS	Difference
All Patients	**250**	**2011**	**350**	**2024**	**88.1%**	**82.7%**	**+ 5.4%**
Cohort							
No Chemotherapy TEXT	40	492	59	499	93.2%	89.1%	+ 4.1%
No Chemotherapy SOFT	33	447	42	445	92.7%	91.3%	+ 1.4%
Chemotherapy TEXT	105	661	144	656	84.6%	77.7%	+ 6.9%
Prior Chemotherapy SOFT	72	411	105	424	83.1%	73.9%	+ 9.2%



DRFI

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DRFI E+OFS	8-Year DRFI T+OFS	Difference
All Patients	**144**	**2011**	**209**	**2024**	**93.0%**	**89.6%**	**+ 3.4%**
Cohort							
No Chemotherapy TEXT	16	492	20	499	97.2%	96.5%	+ 0.7%
No Chemotherapy SOFT	5	447	9	445	99.3%	98.3%	+ 1.0%
Chemotherapy TEXT	70	661	98	656	89.6%	84.6%	+ 5.0%
Prior Chemotherapy SOFT	53	411	82	424	86.8%	79.8%	+ 7.0%

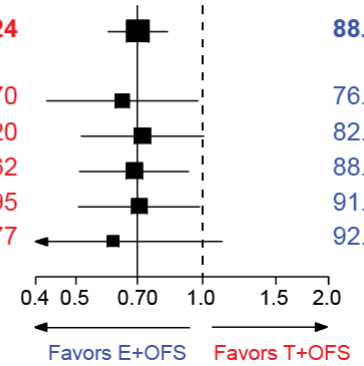


- Consistent relative treatment effects in all cohorts
- Larger absolute benefits of E+OFS in chemo cohorts
- Overall Survival HR=0.86 (0.68-1.10)

Treatment Effect by Age (HER2-neg)

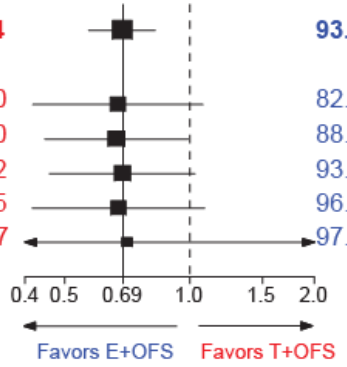
DFS

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DFS E+OFS	8-Year DFS T+OFS	Difference
All Patients	**250**	**2011**	**350**	**2024**	**88.1%**	**82.7%**	**+ 5.4%**
Age at Randomization							
< 35	38	180	54	170	76.9%	68.7%	+ 8.2%
35 - 39	63	333	77	320	82.7%	75.6%	+ 7.1%
40 - 44	72	641	106	662	88.6%	83.8%	+ 4.8%
45 - 49	58	657	87	695	91.9%	87.4%	+ 4.5%
50+	19	200	26	177	92.6%	86.2%	+ 6.4%



DRFI

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DRFI E+OFS	8-Year DRFI T+OFS	Difference
All Patients	**144**	**2011**	**209**	**2024**	**93.0%**	**89.6%**	**+ 3.4%**
Age at Randomization							
< 35	30	180	40	170	82.5%	74.9%	+ 7.6%
35 - 39	42	333	58	320	88.1%	82.5%	+ 5.6%
40 - 44	39	641	59	662	93.5%	90.7%	+ 2.8%
45 - 49	27	657	44	695	96.3%	93.7%	+ 2.6%
50+	6	200	8	177	97.9%	95.3%	+ 2.6%



Randomized Comparison of Adjuvant Tamoxifen plus Ovarian Function Suppression vs Tamoxifen in Premenopausal Women with HR+ Early Breast Cancer: Update of the SOFT Trial

Gini Fleming, MD

on behalf of SOFT Investigators and

International Breast Cancer Study Group (IBCSG)

SOFT: Suppression of Ovarian Function Trial

Enrolled: Dec 2003-Jan 2011

Stratification

Receipt of (neo)adjuvant chemotherapy

-No chemo, enrolled within 12 weeks of surgery (47%)
-Prior chemo, premenopausal E2 level within 8 months (53%)

Nodal status

-Positive (34.5%)

OFS method intended

-Triptorelin (91%)

RANDOMIZE

Median follow-up 8 years

Tamoxifen x 5y (n=1018)

Tamoxifen+OFS x 5y (n=1015)

Exemestane+OFS x 5y (n=1014)

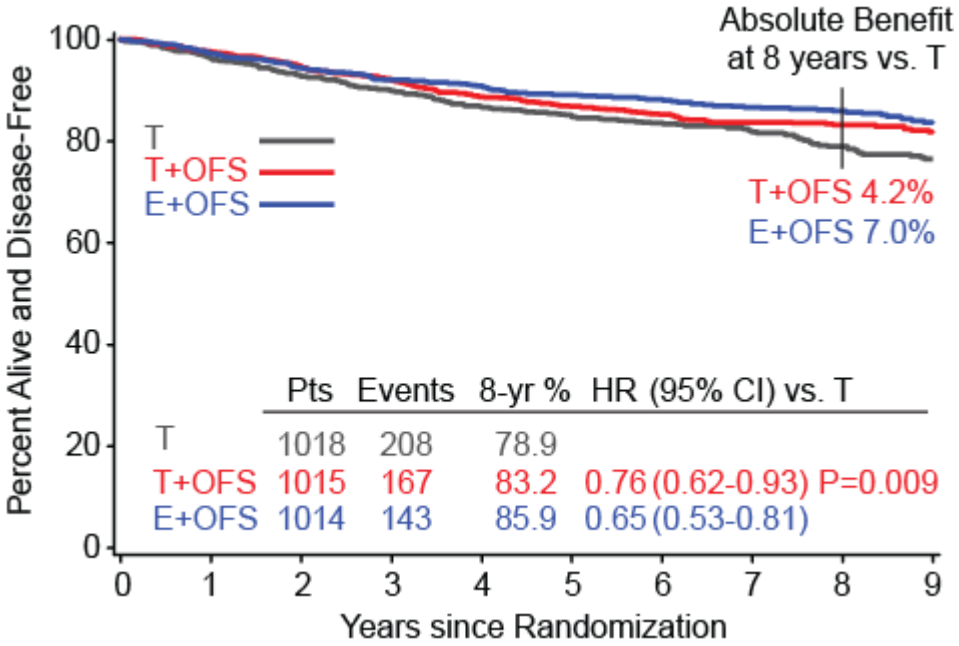
OFS=Ovarian Function Suppression

Patient Characteristics

	No Chemotherapy N=1419	Prior Chemotherapy N=1628	All N=3047
Age (median)	46 yr	40 yr	43 yr
<35 years	**1.5%**	**20.2%**	11.5%
Nodal status			
positive	**8.8%**	**56.9%**	34.5%
negative	91.2%	43.1%	65.5%
Grade			
1	39.7%	13.8%	25.9%
2	52.8%	49.5%	51.0%
3	**6.5%**	**33.7%**	21.0%
HER2+	**3.7%**	**19.2%**	12.0%

SOFT DFS

8 years median follow-up



T+OFS significantly improves DFS vs T-alone in the overall population

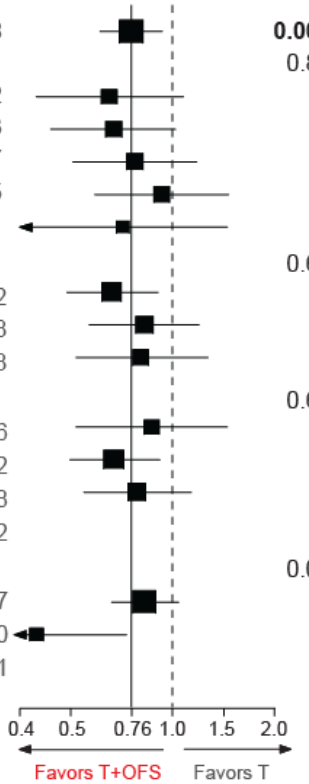
SOFT DFS

8 years median follow-up

	8-yr DFS T	8-yr DFS T + OFS	HR: T + OFS vs T	8-yr DFS E + OFS	HR: E + OFS vs T
All	**78.9%**	**83.2%**	0.76 (0.62-0.93)	**85.9%**	0.65 (0.53-0.81)
No chemo	**87.4%**	**90.6%**	0.76 (0.52-1.12)	**92.5%**	0.58 (0.38-0.88)
Prior chemo	**71.4%**	**76.7%**	0.76 (0.60-0.97)	**80.4%**	0.68 (0.53-0.88)
<35 years (n=350)	**64.3%**	**73.0%**	0.66 (0.41-1.07)	**77.4%**	0.52 (0.31-0.87)

SOFT DFS: According to Subgroups

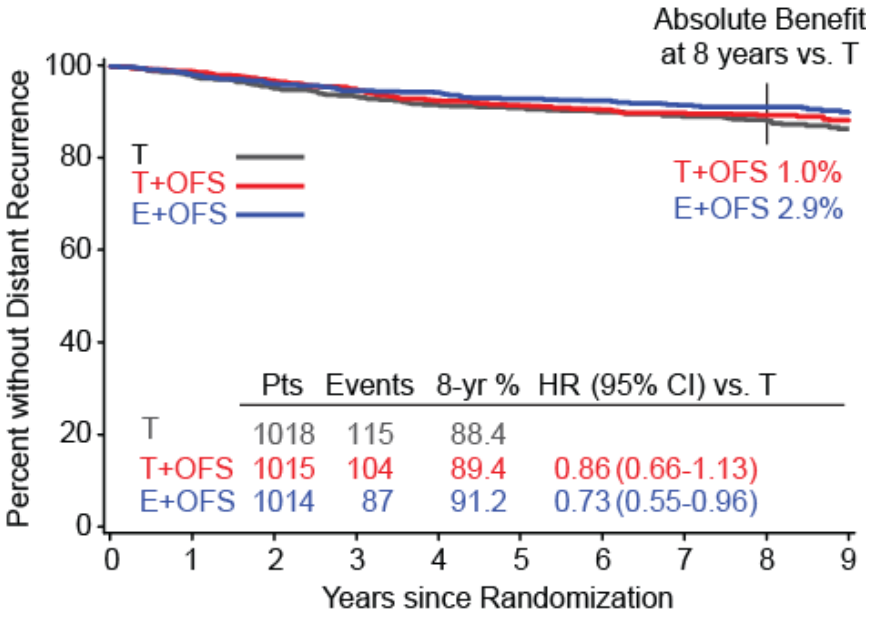
	T+OFS Events	T+OFS Pts	T Events	T Pts	P-Value
All Patients	**167**	**1015**	**208**	**1018**	**0.009**
Age at Randomization					0.82
< 35	30	121	37	112	
35 - 39	40	184	56	203	
40 - 44	43	311	54	307	
45 - 49	40	301	42	305	
50+	14	98	19	91	
Lymph Node Status					0.63
pN0	73	662	103	112	
pN+ 1-3	53	257	64	258	
pN+ 4+	41	96	41	98	
Tumor Grade					0.66
1	29	266	34	276	
2	78	518	101	492	
3	57	212	69	228	
Unknown	3	19	4	22	
HER2 Status					0.04
Negative	147	868	168	117	
Positive	16	119	31	860	
Unknown	4	28	9	41	



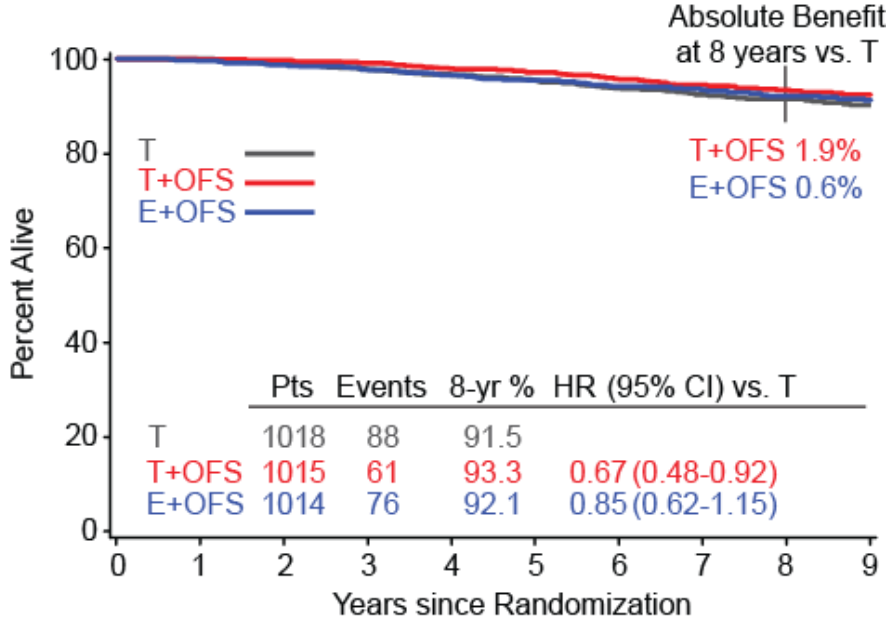
61% of HER2+ received trastuzumab

SOFT Secondary Endpoints

Distant Recurrence-Free Interval



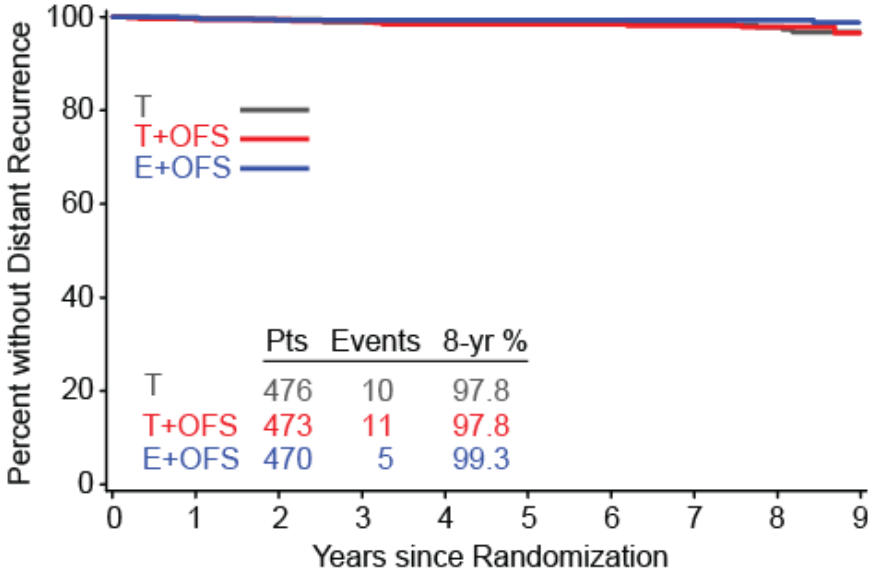
Overall Survival



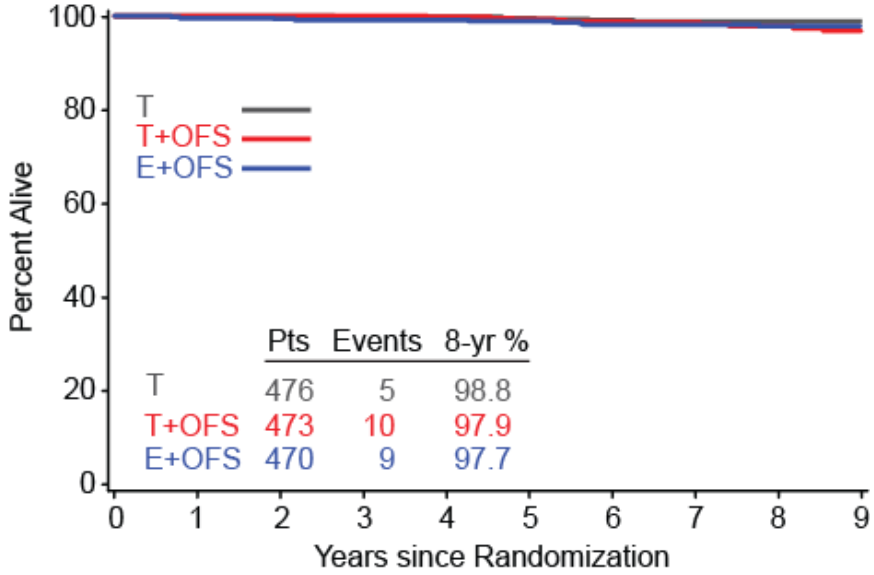
A small overall survival benefit is seen with T+OFS vs T, at 8 yrs median follow-up

SOFT Secondary Endpoints: No Chemo

Distant Recurrence-Free Interval



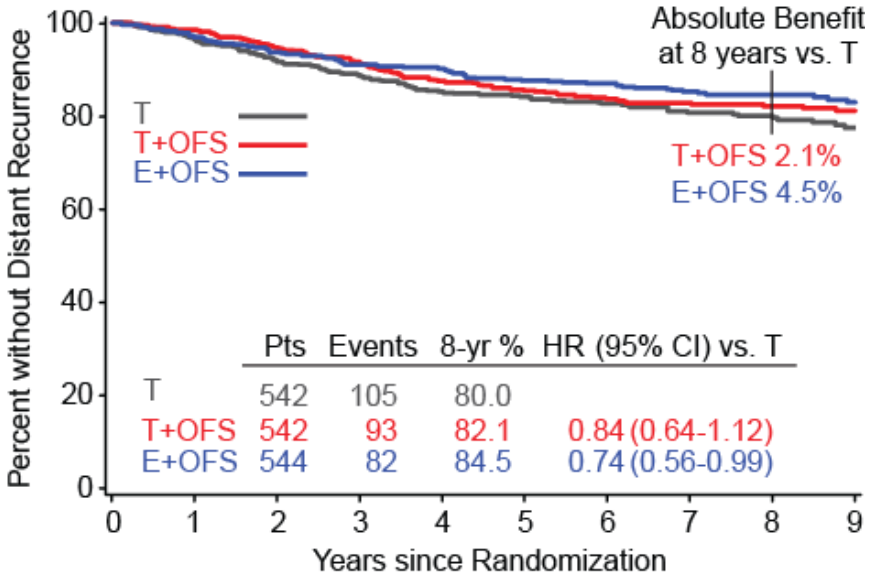
Overall Survival



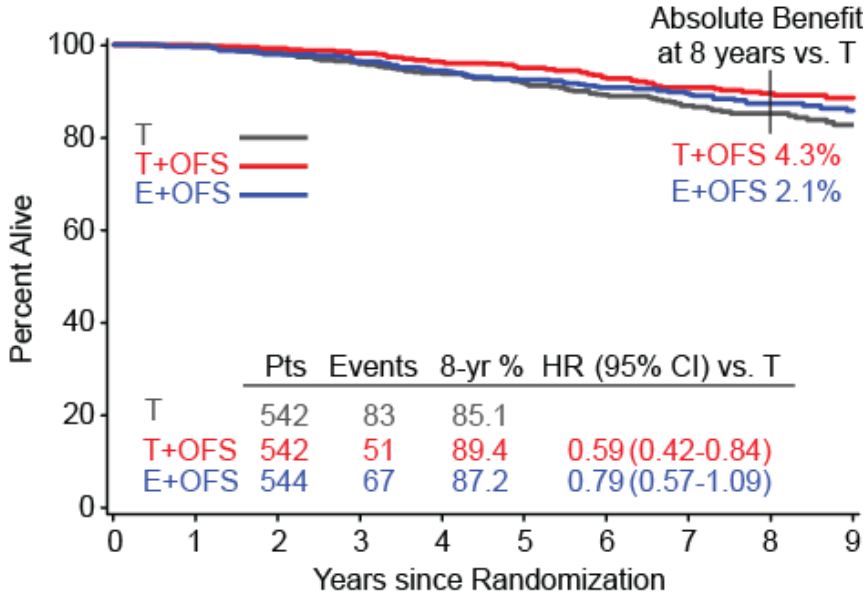
No Chemo cohort remains at low risk of distant recurrence with T alone; 12 of 24 deaths were in setting of no distant recurrence

SOFT Secondary Endpoints: Prior Chemo

Distant Recurrence-Free Interval



Overall Survival



Prior Chemo cohort has small absolute OS improvements in OFS arms at 8 yrs

Protocol and Non-protocol Therapy

	T	T + OFS	E + OFS
Stopped assigned oral endocrine therapy early	22.5%	18.5%	27.8%
Stopped triptorelin early*		21.4%	19.6%
Received OFS (in first 5 yrs)	15.5%		
Used oral endocrine therapy at ≥6 yr**	24.7%	24.3%	12.6%

*and did not undergo oophorectomy or ovarian irradiation
**as adjuvant therapy; denominator is patients alive and in follow-up at 6 yrs

Selected Adverse Events

	T (N=1005)	T + OFS (N=1006)	E + OFS (N=1000)
Endometrial cancer (n)	**N=7**	**N=4**	N=3
Thrombosis/embolism (G2-4)	**2.2%**	**2.2%**	0.9%
Hot flashes (G3)	7.8%	**13.2%**	**10.7%**
Libido decrease (G2)	11.5%	**15.9%**	**17.5%**
Musculoskeletal symptoms (G3-4)	6.7%	5.9%	**12.0%**
Osteoporosis (G2-4; T score<-2.5)	3.9%	6.1%	**11.9%**
Depression (G3-4)	4.1%	4.5%	3.9%

Conclusions: SOFT/TEXT combined analysis

- After longer follow-up (median 9 years), adjuvant E+OFS, compared with T+OFS, shows a sustained absolute improvement in DFS (4%) and reduction in distant recurrence (2.1%).
- Benefit greatest of E+OFS in HER2-negative patients who receive chemo (7-9% absolute improvemnet in DFS)
- Benefit increases with younger age
- No difference in OS between E+OFS and T+OFS, data maturing

Conclusions: SOFT

- At 8 years median f/u T+OFS vs T significantly improves DFS in overall study population (chemo and no chemo)
  - DFS outcomes further improved with E+OFS
  - Greatest benefit seen in patients receiving prior chemo and under 35 (13% absolute benefit with OFS+E vs T)
- 98-99% of no chemo group was free of distant recurrence.
- Small OS benefit is seen at 8 yrs with OFS+T vs T
  - Benefit in prior chemo group
- Treatment must be balanced with toxicity. 28% of patients on AI stopped early. 20% of patients on OS stopped early.

Take Home: Premenopausal women

- If low clinical risk → tamoxifen alone
  - SOFT no chemo group: median age 46 (90% >=40), 91% node neg, 85% T1, 40% grade 1
- If high clinical risk → start with OS/AI. If side effects, try OS/Tamoxifen before switching to Tamoxifen alone
  - Chemo should not be the only determinant of high clinical risk
- If <35 → start OS/AI
- ?HER2
- ?how does pCR influence our assessment of clinical risk

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